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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/580,615	05/23/2007	John W. Benbow	PC026084A	5563

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PFIZER INC.
PATENT DEPARTMENT, MS8260-1611
EASTERN POINT ROAD
GROTON, CT 06340

EXAMINER	
SHTERENGARTS, SAMANTHA L	

ART UNIT	PAPER NUMBER
1626	

NOTIFICATION DATE	DELIVERY MODE
09/12/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

~IPGSGro@pfizer.com

Office Action Summary	Application No.	Applicant(s)	
	10/580,615	BENBOW ET AL.	
	Examiner	Art Unit	
	Samantha L. Shterengarts	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 July 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10* is/are pending in the application.

4a) Of the above claim(s) *6-7, 8a, and 9-10* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5 and 8b* is/are rejected.

7)☒ Claim(s) *8a and 8b* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *26 September 2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Priority

1. The instant application is a national stage entry of PCT/IB04/03749, filed November 15, 2004.

Information Disclosure Statement

2. The information disclosure statements (IDS) submitted on August 21, 2007 and March 19, 2008 were in compliance with the provisions of 37 CFR 1.97 and 37 CFR 1.98. The IDS documents were considered. A signed copy of each form 1449 is enclosed herewith.

Election/Restriction

3. Applicant's election of Group I in the reply filed on July 17, 2008 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Additionally, Applicant's election of the species of example 165 is acknowledged.

As per MPEP 803.02, the Examiner will determine whether the entire scope of the claims is patentable. The elected species was found free of the art; however, The entire scope of the claims was not found to be allowable. As per the MPEP, claims to all other nonelected inventions will be held withdrawn from further consideration.

Status of Claims

4. Claims 6-7, 8a, and 9-10 are withdrawn for being drawn to a nonelected invention. Claims 1-5 and 8b will be examined on their merits.

Claim Objections

5. The numbering of claims is not in accordance with 37 CFR 1.126 which requires the original numbering of the claims to be preserved throughout the prosecution. When claims are canceled, the remaining claims must not be renumbered. When new claims are presented, they must be numbered consecutively beginning with the number next following the highest numbered claims previously presented (whether entered or not). In the instant case, there are two claims numbered 8.

Misnumbered claims 8 been renumbered 8a and 8b.

Claim Rejections - 35 USC § 112

(First Paragraph-Enablement)

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

As stated in the MPEP 2164.01(a), "There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue."

In *In re Wands*, 8 USPQ2d 1400 (1988), factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have need described. They are:

1. The nature of the invention

2. The state of the prior art
3. The predictability or lack thereof in the art
4. The amount of direction or guidance present
5. The presence or absence of working examples
6. The breadth of the claims
7. The quantity of experimentation needed, and
8. The level of skill in the art

5. Claims 1-5 and 8b are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compounds of the Formula (I) and pharmaceutically acceptable salts thereof, does not reasonably provide enablement for prodrugs thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and, concomitantly, to use the invention commensurate in scope with these claims.

The Nature of the Invention

The instant invention is drawn to a compound of the Formula (I), pharmaceutically acceptable salts thereof, and prodrugs thereof. Finding a prodrug is an empirical exercise. Predicting, e.g., if a certain compound is in fact a prodrug that produces the active compound metabolically at a therapeutic concentration and a useful rate, is filled with experimental uncertainty. Attempts have been made to predict drug metabolism *de novo,* but this is still an experimental science. A prodrug of a compound must meet three tests. It must itself be biologically active. It must be metabolized to a second substance *in vivo* at a rate and to an extent to produce that second substance at a physiologically meaningful concentration. Thirdly, that second substance must be biologically active. Determining whether a particular compound meets these three criteria requires a clinical trial setting and a large quantity of experimentation.

The State of the Prior Art

"Pro-drugs" are commonly known in the art as drugs which are administered in an inactive (or less active) form, and then metabolized in vivo into an active metabolite. As disclosed in Stella (Expert Opinions *Prodrugs as therapeutics*), "prodrugs are bioreversible derivatives of drug molecules used to overcome some barriers to the utility of the parent drug molecule. These barriers include, but are not limited to, solubility, permeability, stability, presystemic metabolism, and targeting limitations" (277). Stella, Valentino J, Expert Opinion of Therapeutic Patents, *Prodrugs as therapeutics*, 2004 14(3): 277-280. Wolff et al. (Burger's Medicinal Chemistry, 5th Ed., Vol. 1, pgs. 975-977, 1994) summarizes that state of the prodrug art, the lengthy research involved in successfully identifying a prodrug, and difficulties of extrapolating between species. With the limited direction and exemplification the specification offers, it is highly unpredictable that the compounds of the Formula (I) will actually form effective prodrugs. Testa, Bernard, Biochemical Pharmacology, *Prodrug Research: futile or fertile?* 68 (2004) 2097-2106, discloses, on page 2098, the various challenges in prodrug research, concluding that all of these challenges may render prodrug optimization difficult to predict and achieve. Finally, Ettmayer, Peter, Medicinal Chemistry, *Lessons Learned from Marketed and Investigational Prodrugs,* 47(10) (2004) 2394-2404, discloses, on page 2401, that "the prodrug strategy should only be considered as a last resort to improve the oral bioavailability of important therapeutic agents" and "At the beginning of each prodrug program, there should be a clear definition of the problem to solve and defect to improve. The prodrug approach should not be misunderstood as a universal solution to all barriers to a drug's usefulness, and on page 2402, "The majority of all prodrug approaches face the challenge of identifying the optimal prodrug plus its activation system to enhance or prolong the

concentration of the active principle at the site of action. Because of the complex situation of prodrug transport and processing, we recommend, especially for novel prodrug principles, that the first step should be to design and investigate different prodrug prototypes of high diversity (different attachment sites, linkers, promoieties, hydrolytic, oxidative, reductive activation, chemical vs. enzymatic activation)." Ettmayer et al. concludes that "the focus on victorious prodrugs should not be misunderstood as neglecting the inherent difficulties and additional layers of complexity a prodrug strategy might face." The evidence supports the conclusion that the method of making claimed prodrugs is a subject for further study and experimentation.

The Level of Skill in the Art and the Predictability or lack thereof in the art

The level of skill of the pharmacological art involves screening in vitro and in vivo to determine which compounds exhibit the desired pharmacological activities as prodrugs. There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any prodrug on its face, without evidence to support that particular prodrug. It is noted that the pharmaceutical art is unpredictable and requires the embodiments to be individually assessed for physiological activity. Thus, the more unpredictable the art, the more information in support of the invention is required to satisfy the statute. See *In re Fisher*, 427 F.2d 833, 166 USPQ 18 (CCPA 1970). Each embodiment of a prodrug must be supported by this invention in order to be enabled for the full range of prodrugs of compounds of the Formula (I).

The Amount of Direction or Guidance Present

The specification discloses in ¶ [0057] that "The term "prodrug" refers to a compound that is a drug precursor which, following administration, releases the drug in vivo via a chemical or physiological process (e.g., upon being brought to physiological pH or through enzyme activity). A discussion of the preparation and use of prodrugs is provided by T. Higuchi and W. Stella, "Prodrugs as Novel Delivery Systems, Vol. 14 of the ACS Symposium Series, and in Bioreverible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987." This disclosure is directed to any pharmaceutically acceptable prodrug; however, as discussed above, it would be necessary for Applicant to provide evidentiary support for each embodiment due to the unpredictability in the art with regards to the success of prodrugs with some drugs over others. There are no working examples in the specification that show how to make or use prodrugs of the instantly claimed compounds. Additionally, the lack of examples in the specification is not sufficient to enable one skilled in the art to which it pertains to make and use any pharmaceutically acceptable prodrug as interpreted broadly by one of ordinary skill in the art. The specification does not adequately enable a method of making all prodrugs of the compounds that the claims encompass, as defined in the instant specification. The specification has limited exemplification thereof and of the necessary starting materials, as discussed *supra*.

As stated in Morton International Inc. v. Cardinal Chem, Co., 28 USPQ2d 1190:

> [T]he specification purports to each, with over fifty examples, the preparation of the claimed compounds with the required connectivity. However... there is no evidence that such compounds exist... the examples of the patent do not produce the postulated compounds..., there is...no evidence that such compounds even exist.

The same circumstance is true here.

The Breadth of the Claims

The claims are drawn to any compound which is converted to a therapeutically active compound after administration, and the term should be interpreted as broadly in the instant application as is generally understood in the art. As discussed above, this broad disclosure cannot possibly enable one skilled in the art to which it pertains to make and use any pharmaceutically acceptable prodrug due to the unpredictability in the art with regards to the success of prodrugs with some drugs over others.

The specification provides limited support, as noted above, for the large number of prodrugs encompassed by the claims. The quantity of experimentation needed to make and use all of the prodrugs encompassed by the claims would be an undue burden on one skilled in the chemical art, since the skilled artisan is given inadequate guidance for the reasons state above. Even with the undue burden of experimentation, there is no guarantee that one would obtain the desired prodrugs in view of the Wolff reference.

This discussion established *prima facie* non-enablement. Cancellation of "prodrug" from the claims would overcome this rejection.

The Quantity of Experimentation Needed

Based on the unpredictable nature of the invention and the state of the prior art and the breadth of the claims, one of ordinary skill in the pertinent art would be burdened with undue experimentation study to determine whether any pharmaceutically acceptable prodrug of compounds of the Formula (I) would successfully act as prodrugs as they are known in the art. Therefore, in view of the Wands factors discussed above, to practice the claimed invention herein, a person of skill in the art would have to engage in undue experimentation to test which

prodrugs, if any, would produce desired activity with compounds of the Formula (I) with no assurance of success.

Conclusion

6. No claims are allowed.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Samantha Shterengarts whose telephone number is (571)270-5316. The examiner can normally be reached on Monday thru Thursday 9-6pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. Joseph K. McKane can be reached on 571-272-0699. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Samantha L. Shterengarts/
Examiner, Art Unit 1626

/Kamal A Saeed, Ph.D./
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